

Evidence-Based Medicine

2013.0114

腫瘤外科 R1 高捷妮

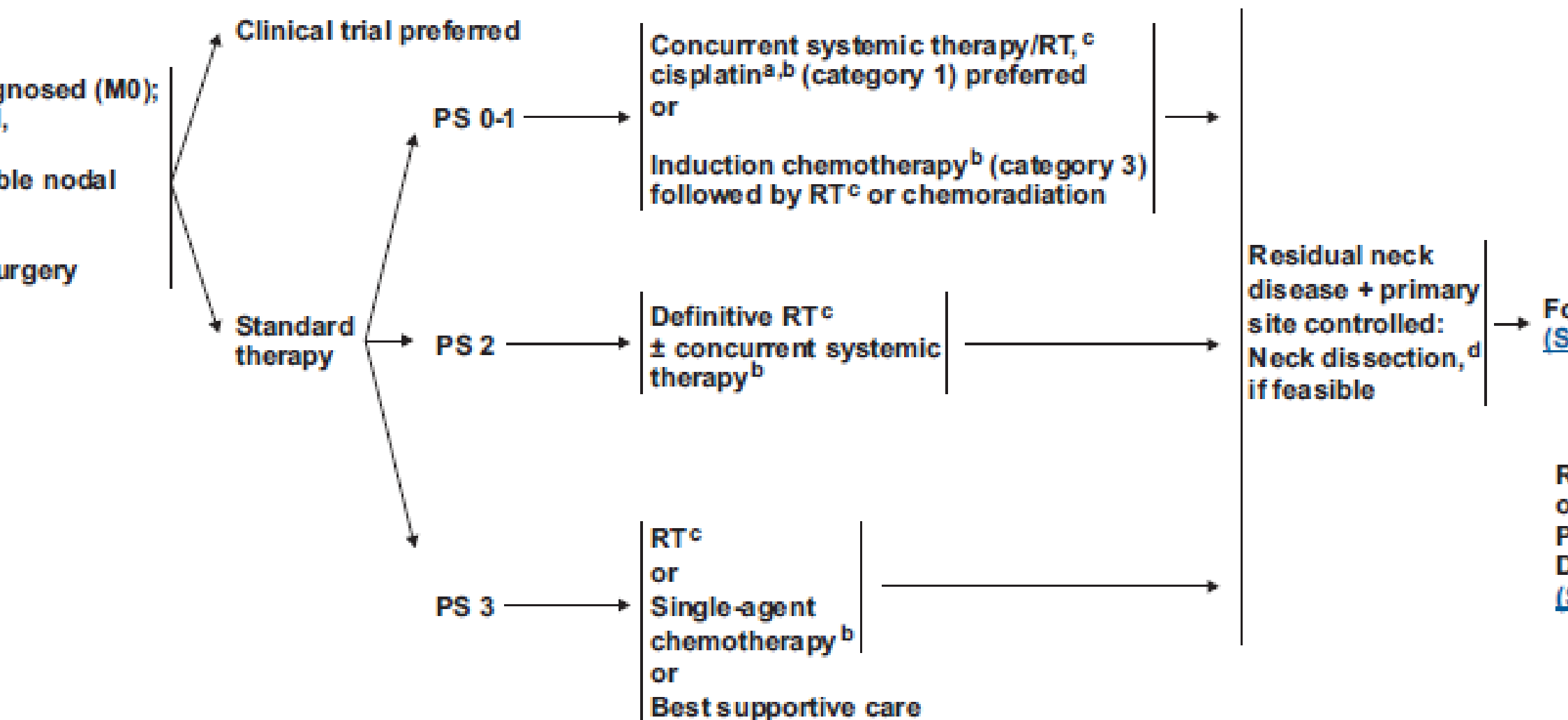
Clinical Scenario

A 64-year-old male has the history of

- ▶ Recurrent left buccal cancer post neck resection and radiotherapy

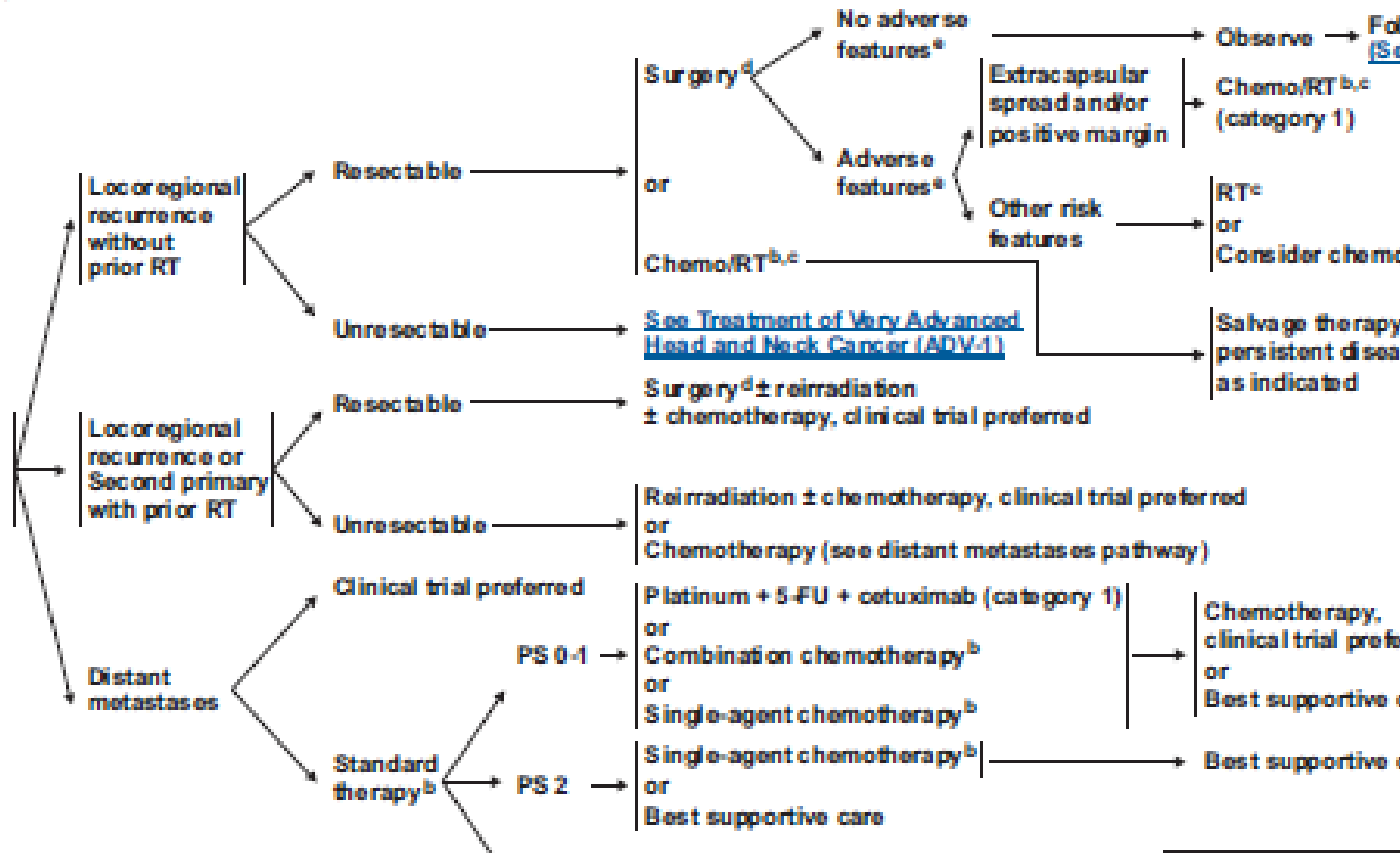
Background Questions

Treatment for advanced oral cancer



S

TREATMENT OF HEAD AND NECK CANCER



Background Questions

Does patient with advanced head and neck tumor should need ?

Patient	With advanced head and neck tumor
Intervention	IAIC
Comparison	Without further chemotherapy
Outcome	Survival rate, disease free interval, morbidity

Search Database

- ▶ Keyword:
 - ▶ Advanced head and neck tumor, IAIC
- ▶ Database:
 - ▶ DynaMed
 - ▶ ACP journal club
 - ▶ Cochrane library
 - ▶ UpToDate
 - ▶ PubMed



Search Result

CoCrane Library: none was found

ACP journal club: none was found

DynaMed: none was found

Intra-Arterial Chemotherapy for Head and Neck Cancer

Is There a Verdict?

1. Robbins KT, Howell SB, Williams JS. Intra-arterial chemotherapy for head and neck cancer: is there a verdict? *Cancer*. 2010;116:2068-2070.
2. Rasch CR, Hauptmann M, Schornagel J, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial. *Cancer*. 2010;116:2159-2165.
3. Doweck I, Denys D, Robbins KT. Tumor volume predicts outcome for advanced head and neck cancer treated with targeted chemoradiotherapy. *Laryngoscope*. 2002;112:1742-1749.

Coen R. N. Rasch, MD, PhD

*The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital
Amsterdam, The Netherlands*

With interest which questioned the conclusion of a prospective randomized trial² in which intra-arterial (IA) cisplatin chemoradiation was not found to be superior to the current standard of intravenous cisplatin chemoradiation.

If the tumor exceeded >1 cm over the anatomical midline, double-sided infusion according to the flow ratio between the 2 feeding arteries was recommended.

- ▶ The lower rate of double-sided infusions in earlier phase may therefore be attributed to a different patient selection.
- ▶ The difference in mean tumor volume of 18 mL versus 30 mL between the 2 series is indicative in that respect

whose primary tumor volume exceeded a total of 30 mL.

It is striking to observe that local control was significantly better in the IA group compared with the intravenous group among this cohort of patients (hazard ratio [HR], 0.17; 95% confidence interval [95% CI], 0.05-0.60 [P = .0025]).

Although this benefit from IA treatment was limited to the 1 of 26 patients with a large (>30 mL) tumor not extending across the midline (HR, 0.14; 95% CI, 0.03-0.72), no significant benefit was observed in the remaining 3 groups.

[Onkologie](#). 2004 Dec;27(6):547-51.↵

Selective high-dose intra-arterial cisplatin as palliative treatment for incurable head and neck cancer.↵

[Teymoortash A](#), [Bien S](#), [Dalchow C](#), [Sesterhenn A](#), [Lippert BM](#), [Werner JA](#).↵

Source↵

Department of Otolaryngology, Head and Neck Surgery, Philipps University of Marburg, Germany. teymoort@med.uni-marburg.de↵

8 patients with advanced residual or recurrent squamous cell carcinoma of the head and neck were evaluated.

These patients were included in the present study particularly because of progredient pain and recurrent bleedings due to tumor progression.

In addition 6/8 patients suffered from unpleasant tumor-related smell. All patients received simultaneous infusions of cisplatin (150 mg/m²) intra-arterially to the tumor and sodium thiosulfate intravenously (9 g/m²) for systemic neutralization of cisplatin.

The patients were treated by at most 4 cycles of selective intra-arterial chemotherapy via femoral approach.

RESULTS

8 patients with advanced residual or recurrent squamous cell carcinoma of the head and neck were evaluated.

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The patients were treated by at most 4 cycles of selective intra-arterial chemotherapy via femoral approach.

Tumor-associated pain, occurrence of tumor bleeding and tumor-related smell were reduced after at least 2 cycles of intra-arterial chemotherapy in all patients.

Clinical and radiological assessment of the primary tumor size revealed a partial response in 4 patients while 4 patients were classified as nonresponders. Intra-arterial cisplatin treatment was well tolerated.

Oral Oncology 46 (2010) 860–863



ELSEVIER

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology



Preselective intra-arterial chemoradiotherapy with docetaxel–nedaplatin in advanced oral cancer

Yasuhiro Kobayashi ^{a,*}, Beng Gwan Teh ^{a,c}, Hirotaka Sakaki ^a, Hisashi Sato ^a, Hiroto Kimura ^a, Sinya Kakehata ^b,
Masahito Nagahata ^b

^a Department of Oral and Maxillofacial Surgery, Hirosaki University Graduate School of Medicine, 5-Zaiju-cho, Hirosaki 036-8562, Japan

^b Department of Radiology, Hirosaki University Graduate School of Medicine, 5-Zaiju-cho, Hirosaki 036-8562, Japan

^c Department of Oral and Maxillofacial Surgery, Misawa City Hospital, 1-10 Chuou-cho, 4-Chome, Misawa 033-0001, Japan

Cisplatin-based, superselective, intra-arterial chemotherapy concurrent with radiotherapy (SSIACRT) has gained wide acceptance as a common/curative treatment for advanced head and neck cancer.

We combined nedaplatin (CDGP) with docetaxel (DOC) as a new combination in SSIACRT for advanced oral squamous cell carcinoma in 2003. Twenty-two patients with advanced oral cancer were treated by radiotherapy (66 Gy) concurrent with superselective intra-arterial DOC (40 mg/body) and CDGP (80 mg/m²) infusion between 2003 and 2009. Complete response was achieved in 18 (81.8%) of the 22 patients.

Of the 17 patients with positive neck disease, 16 (94%) were assessed as disease-free. The 5-year overall survival rate was 78.5%, and the major adverse effects were leukocytopenia and mucositis.

Five patients (22.7%) developed distant metastases post-treatment.

These results indicate that intra-arterial docetaxel – nedaplatin infusion concurrent with radiotherapy is efficacious for advanced oral cancer. The side effects are easily manageable, and the most important outcome of the treatment is the preservation of patients' quality of life (QOL) and improved prognosis.

Superselective intra-arterial infusion of cisplatin (CDDP) with concomitant radiotherapy (RADPLAT) was reported to be a promising treatment by Robbins et al.[1] It has been reported to have an 80% complete response rate in advanced head and neck cancer. RADPLAT has also been reported to be effective for the control of bulky nodal disease (N2-3), with a complete response rate of 66%. Since the reports of RADPLAT, superselective intra-arterial chemotherapy concurrent with radiotherapy (SSIACRT) has been widely accepted, and various combinations of anticancer drugs have been introduced.

The purpose of this report was to determine the efficacy of two anticancer agents, docetaxel (DOC) and nedaplatin (cis-diammine-glycolate platinum, CDGP), as a combination in SSIACRT for advanced oral cancer.

Patients and methods

Twenty-two patients (14 men, 8 women; age, 27 – 86 years; median age, 61.7) with advanced oral cancer were treated between 2003 and 2009 at the Department of Oral and Maxillofacial Surgery, Hirosaki University Hospital.

All patients had previously untreated disease. All tumors were histologically confirmed squamous cell carcinoma (SCC).

- ▶ The site of disease was the tongue in 6 patients, lower gum in 5 patients, upper gum in 5 patients, floor of the mouth in 3 patients, buccal mucosa in 2 patients, and maxillary sinus in 1 patient.
- ▶ One patient with carcinoma of the floor of the mouth had simultaneous esophageal cancer as multiple primary cancers.

After consultations amongst oral surgeons, radiation oncologists, and medical oncologists, SSIACRT was performed prior to treatment for esophageal cancer.

reatment procedure

The extent of tumor invasion was assessed by computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography CT (PET-CT).

Primary tumor and all nodal areas were irradiated to 50 Gy in 25 fractions, 5 fractions a week, over a period of 5 weeks, immediately followed by a boost of 16 Gy in 8 fractions to all involved areas, including the primary tumor (total dose 66 Gy).

All patients received 3 times concurrent intra-arterial DOC (40 mg/mm²) and CDGP (80 mg/mm²) infusion every 4 weeks in the following manner.

All catheterizations were performed using the standard Seldinger technique via the femoral artery. The diagnostic angiographic procedure was routinely performed with a 4.0-Fr angio catheter (Phenx Type HIGA-A1, Create medic, Yokohama, Japan).

After performing common carotid angiography to assess the bifurcation of the carotid artery and the origin of the feeding artery, the coaxial technique was used to place a 2.1-Fr microcatheter (Tangent, Boston Scientific, Natick, MA, USA) in the feeding artery using a .016-inch, 180-cm guide wire (Radifocus guide wire, Terumo, Tokyo, Japan).

A microcatheter was placed in the appropriate feeding artery of the primary tumor, and DOC and CDGP were then infused through the microcatheter.

To identify the feeding vessels, CT angiography (CTA) was performed with combined CT and angiography. DOC and CDGP were injected at rates of 1 – 2 mg/min and 5 – 7.5 mg/min, respectively.

In patients with bulky nodal diseases, who were confirmed to have feeding arteries, anticancer drugs were partially delivered to the regional neck area as well.

When the feeding arteries were multiple, the dose of drug for each feeder was determined by the percentage of tumor enhancement on CTA.

When the number of feeding arteries was more than 4 or the feeding artery was not identified by microcatheter, an arterial redistribution technique was used.

Unnecessary branches of the ECA were embolized with micro-coils (Trufil Pushable coil, Codman, Raynham, MA, USA and Tornade Embolization Microcoil, Cook, Bloomington, IN, USA) via microcatheter.

The procedure was performed within the extent of the ECA. The drug infusion procedure was performed in the radiology suite by interventional radiologists

Primary tumor site	Age/sex	T	N	Selected artery (embolized artery)*	IA courses	Results	Primary recurrence	Neck recurrence	Treatment after SSIACRT	Distant meta	Survival period/M
Lower gum	44/F	4	2c	FA, LA, IAA, APA	3	CR					82
Tongue	47/F	4	2a	FA, LA, IAA, APA	3	CR					81
Floor of the mouth	44/M	4	2b	FA, LA, IAA	3	PR			Salvage op	Lung	12
Buccal mucosa	62/M	4	0	MA	2	CR		+	RND		48
Tongue	79/F	4	2c	ECA (STA, MA)*	3	CR		+		Lung	41
Tongue	27/M	3	1	LA	2	CR					41
Tongue	76/M	4	1	LA	3	CR				Lung, liver	27
Upper gum	72/F	4	0	MA	3	CR		+		Cavernous sinus	14
Upper gum	69/F	4	2c	MA	2	CR					35
Lower gum	65/F	4	0	FA	2	CR					33
Tongue	75/M	3	0	LA	2	CR					33
Buccal mucosa	72/M	4	1	ECA (STA, OA)*	3	CR					32
Upper gum	86/M	4	1	MA	2	PR			Salvage op		23
Floor of the mouth/esophagus	67/M	2	2a	ECA (STA, OA)*	3	CR					25
Lower gum	59/F	3	0	FA	3	CR	+		Salvage op		23
Lower gum	57/M	4	2b	ECA (STA, OA, IAA)*	3	CR				Lung	5
Tongue	63/M	4	2b	LA, OA	3	CR					18
Floor of the mouth	59/M	2	2c	blt LA, blt FA, OA	3	CR					17
Lower gum	46/M	4	2b	FA, OA	3	PR			Salvage op		13
Upper gum	75/F	4	2c	MA	3	CR					10
Maxillary sinus	60/M	4	1	MA	3	PR			Chemotherapy		10
Upper gum	54/M	4	2b	MA	3	CR					9

valuation of response and toxicity

Responses to therapy were assessed by clinical examination, CT, and MRI 4 weeks after the completion of SSIACRT. FDG-PET was performed 8 weeks after the completion of radiotherapy to avoid false-positive results caused by inflammation.

Biopsy was not performed. Surgical resection of primary residual tumor and/or neck dissection for positive neck disease or chemotherapy alone was performed in patients evaluated as PR.

Salvage tumor excision was performed with a safety margin set from the extension of the residual tumor.

All toxicities encountered during SSIACRT were evaluated according to the National Cancer Institute-Common Toxicity Criteria (Version 3.0, 2004)

Results

Twenty-two patients were enrolled and evaluated in this study.

All patients completed SSIACRT without interruption.

Sixteen patients received three courses of intra-arterial infusion of DOC and CDGP, while 6 had two courses due to a CR assessment or severe nausea and vomiting that resulted in the patients refusing the third intra-arterial infusion.

Of the 22 patients, CR was achieved in 18 (81.8%) and PR in 4 (18.2%) patients. Of the 17 patients with positive neck disease, 16 (94%) were assessed as disease-free.

One patient with persistent primary and neck disease after SSIACRT was subsequently treated by salvage operation (bilateral neck dissection, subtotal glossectomy, segmental resection of the mandible, excision of floor of the mouth, reconstruction), but succumbed to local recurrence and lung metastasis.

Two patients with persistent primary tumor were treated successfully by salvage operation.

Recurrence after SSIACRT

Of the 18 patients who were evaluated as CR, 1 patient had relapse in the primary site 7 months later and was treated successfully by excision of the recurrent tumor.

Three patients developed neck recurrence. One was treated successfully by radical neck dissection. The other 2 with distant metastases received palliative treatment. Distant metastases occurred in 5 patients (22.7%).

toxicity

Twenty-two patients (90.9%) experienced grade 3 – 4 hematologic toxicity consisting of leukocytopenia (n = 19; 86.4%), anemia (n = 4; 18.2%), and thrombocytopenia (n = 1; 4.5%). Mucositis (n = 16; 68.2%) was a non-hematologic side effect that was greater than grade 3.

There were no events of otologic and renal toxicity and no central nervous system complications related to the infusion technique.

Almost all of the patients required opioid analgesics for mucositis and pharyngitis.

One patient developed osteoradionecrosis of the mandible post-treatment.

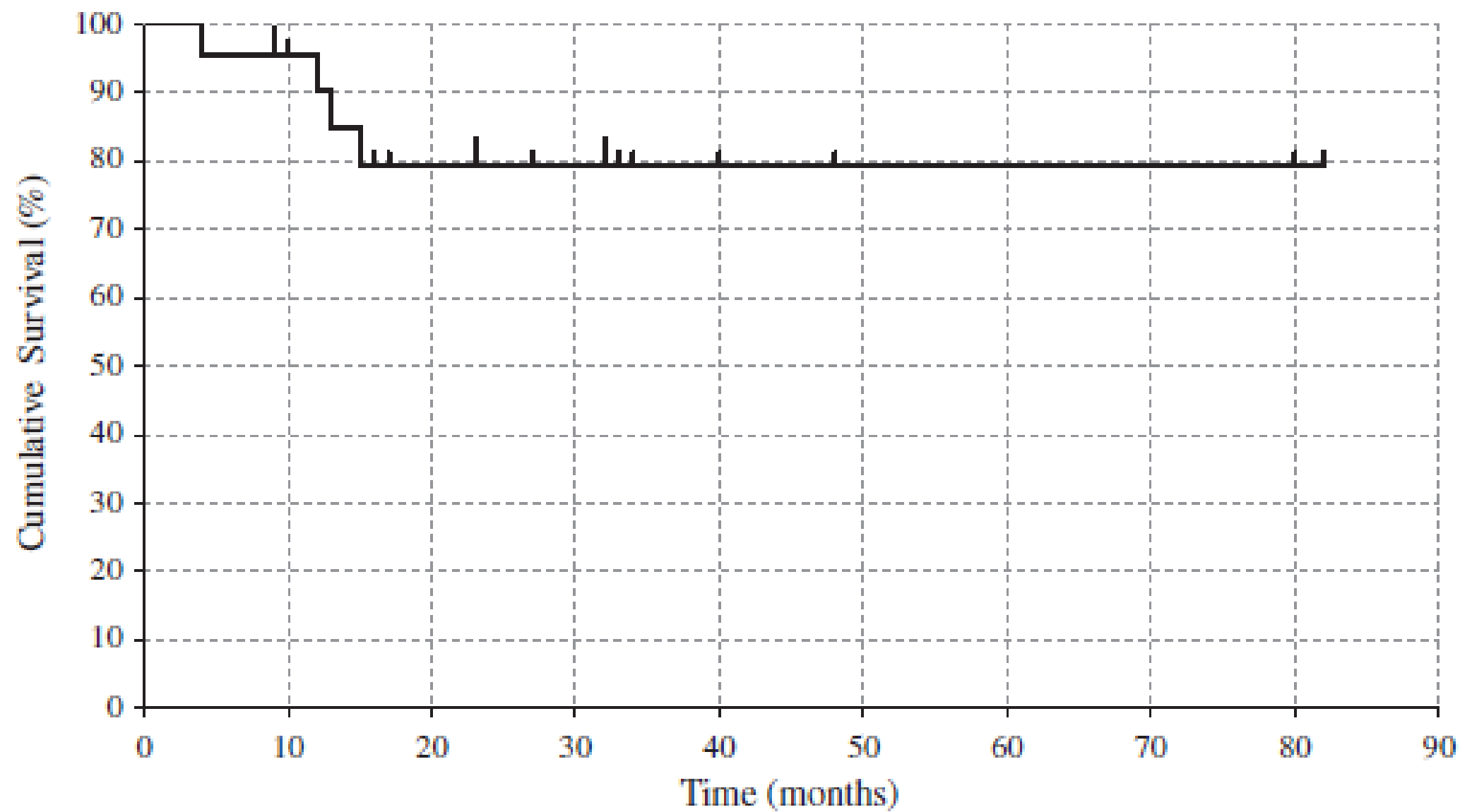
Table 2

Type and distribution of major toxicity events.

Toxicity	Number of patients by toxicity grade			
	I	II	III	IV
Hemoglobin	8	10	4	
Leukocytes		3	14	5
Platelets	17	3	1	
Alopecia				
Mucositis		7	15	
Nausea	7	6		
Vomiting	7	3		

Survival

The 5-year overall survival rate was 78.5%, with a median follow-up duration of 18 months



Discussion

In SSIACRT, two well-established methods have been widely performed: continuous administration of chemotherapeutic agents over a temporal retrograde approach via the superficial temporal artery and repeated bolus infusions over a trans-femoral anterograde approach.

The advantages of the temporal approach are: reduced incidence of technique-related complications to cranial nerves, lower dose of anticancer drugs infused due to the use of daily infusion, and catheterization can be performed by the surgeon alone

In contrast, the advantages of the trans-femoral approach are that it is more selective or superselective, but troublesome and complicated daily management of the catheter is unnecessary.

In our department, intra-arterial chemotherapy was infused via the femoral artery every 4 weeks due to its greater superselectivity and other advantages.

Chemoembolization is a well-established technique combining intra-arterial chemotherapy with delivery of embolic agents to achieve an antitumor effect due to a high local concentration and prolonged dwell time of the drug in the management of liver tumors.

Instead of intra-arterial infusion to various feeding arteries, an arterial redistribution technique by embolization is feasible for oral cancers in which the flow to the outside area of the tumor is stopped.

There are two major complications in arterial redistribution:

- ▶ (1) displacement of micro-coils to the peripheral region, and (2) intimal injury, which was not seen in this study.

There is no possibility of brain infarction by displacement of microcoils because embolization is performed only in the ECA.

Recently, DOC has shown significant single-agent activity in metastatic or recurrent/incurable head and neck SCC, and the addition of 5-fluorouracil – cisplatin to DOC chemotherapy (TPF) offered a survival benefit.

Yabuuchi et al. achieved a better result with intra-arterial infusion therapy by combining CDDP and DOC for recurrent head and neck cancer than with CDDP alone

Recently, CDGP, an analogue of CDDP with less nephrotoxicity that does not require hydration, was reported to be effective for oral cancer treatment.

Due to the advantages, we therefore replaced CDDP with CDGP and combined it with DOC in SSIACRT.

The severe side effects of SSIACRT in this report were grade 3 to 4 leukocytopenia, for which reversion of the leukocyte count was achieved after injection of G-CSF, a grade 3 thrombocytopenia, and mucositis that required no interruption of irradiation.

Considering that the severe side effects encountered by the patients were manageable, and a good treatment effect was obtained, the combination of the two anticancer drugs and the dose applied was thought to be appropriate.

In RADPLAT, CDDP was rapidly infused to selectively encompass only the dominant blood supply of the targeted tumor, and no specific attempt was made to infuse the regional lymph nodes.

Despite no infusion to the regional neck, the CR rate obtained at the nodal region was 88%. The result was similar to ours, with a 94% CR rate.

In our treatment protocol, for patients with bulky nodal disease, anticancer drugs were partially delivered to this region.

From our experience, feeding arteries to level 1 and 2 lymph nodes were the facial artery and branches of the occipital artery; therefore, infusion of anticancer drugs into these arteries was conducted.

In cases with infusion to the occipital artery, an arterial redistribution technique by embolization at peripheral portions of the occipital artery was performed.

Biopsy was not performed to evaluate the treatment effect. This was because blind biopsy might easily fail to detect residual tumor.

Instead of biopsy, all patients underwent FDG-PET before and after treatment. Goerres et al. reported that FDG-PET performed 6 to 8 weeks after completion of combined radiation and chemotherapy in patients with advanced head and neck cancer was suitable for evaluation of treatment.

Our study also showed that FDG-PET, 8 weeks after radiotherapy, was suitable for evaluation of the treatment effect

Distant metastasis was the most common mode of recurrence among patients with advanced head and neck cancer treated with RADPLAT.

Doweck reported that 45 (18%) of the 250 patients who received RADPLAT developed distant metastases, and the result was comparable to our 22.7%.

Vikram et al. reported that 20 (17%) of 114 patients with stage 3 – 4 head and neck cancer treated with a combination of surgery and postoperative radiotherapy developed distant metastases.

considered higher than in the conventional treatment group, but the patients who received SSIACRT were mostly advanced cases.

Furthermore, recent introduction of FDG-PET, a sensitive whole-body imaging technique, has shown potential for early detection of distant metastases.

Further examinations are needed to clarify this matter, and efforts to reduce the risk of distant metastasis are required.

Conflict of interest statement

None declared.

證據等級

Level	與[治療/預防/病因/危害]有關的文獻
1a	用多篇RCT所做成的綜合性分析(SR of RCTs)
1b	單篇RCT(有較窄的信賴區間)
1c	All or none
2a	用多篇世代研究所做成的綜合性分析
2b	單篇cohort及低品質的RCT
2c	Outcome research / ecological studies
3a	SR of case-control studies
3b	Individual case-control studies
4	Case-series(poor quality :cohort / case-control studies)

Appraisal: 嚴格評讀文獻

Are the results of the study valid?

- ▶ Was the assignment of patients to treatment randomized? No
- ▶ Were all patients who entered the trial properly accounted for and attributed at its conclusion? Yes
- ▶ Was follow-up complete? Yes
- ▶ Were patients analyzed in the groups to which they were randomized (intention to treat analysis)? No
- ▶ Were patients, their clinicians, and study personnel “blind” to treatment? No
- ▶ Were the groups similar at the start of the trial? Yes
- ▶ Baseline prognostic factors (demographics, co-morbidity, disease severity, other known confounders) balanced? No
- ▶ Aside from the experimental intervention, were the groups treated equally? Yes

patients ?

- ▶ Can the results be applied to my patient care? **Yes**
 - ▶ Patients similar for demographics, severity, co-morbidity and other prognostic factors? **Yes**
- ▶ Were all clinically important outcomes considered?
 - ▶ **Yes, nearly all**
- ▶ Are the likely treatment benefits worth the potential harms and costs?
 - ▶ **Yes**

Apply

醫療現況	病人意願
用 IAIC	高
生活品質	社會脈絡
對預期高	無

自我評估

我提出的問題是否具有臨床重要性？**是**

我是否明確的陳述了我的問題？

◦ 我的foreground question 是否可以清楚的寫成 PICOT？**是**

我是否清楚的知道自己問題的定位？（亦即可以定位自己的問題是屬於診斷上的、治療上的、預後的或流行病學上的），並據以提出問題？**是，屬於治療範圍**

對於無法立刻回答的問題，我是否有任何方式將問題紀錄起來以備將來有空時再找答案？**有**

自我評估

- 我是否已盡全力搜尋？有
- 我是否知道我的問題的最佳證據來源？是
- 我是否從大量的資料庫來搜尋答案？是
- 我工作環境的軟硬體設備是否能支援我在遇到問題時進行立即的搜尋？是
- 我是否在搜尋上愈來愈熟練了？是
- 我會使用「斷字」、布林邏輯、同義詞、MeSH term，限制（limiters）等方法來搜尋？是
- 我的搜尋比起圖書館人員或其他對於提供病人最新最好醫療有熱情的同事如何？差不多

我評估

- ▶ 我是否將搜尋到的最佳證據應用到我的臨床工作中？**是**
- ▶ 我是否能將搜尋到的結論如NNT, LR用病人聽得懂的方式解釋給病人聽？**有難度**
- ▶ 當搜尋到的最佳證據與實際臨床作為不同時，我如何解釋？**會參考文獻證據但仍以實際臨床狀況，盡量找出對病人最好的方式**

自我評估

- ▶ 當最佳證據顯示目前臨床策略需改變時，我是否遭遇任何阻止改變的阻力？**無**
- ▶ 我是否因此搜尋結果而改變了原來的治療策略？做了那些改變？**沒有**

- ▶ 這篇報告，我總共花了多少時間？
 - ▶ 約十幾個小時
- ▶ 我是否覺得這個進行實證醫學的過程是值得的？
 - ▶ 值得



End of The Presentation



Thanks for attention